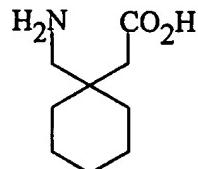


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NOVEL STEREOSELECTIVE PROCESSES FOR THE PREPARATION
OF GABAPENTIN ANALOGUES

BACKGROUND OF THE INVENTION

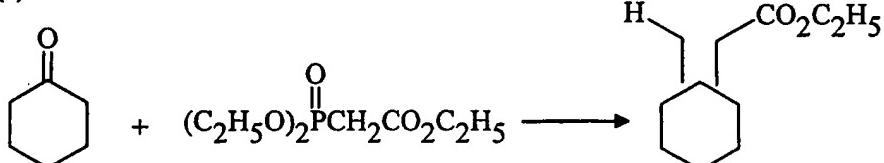
United States Patent Number 5,091,567, hereby incorporated by reference,
5 covers a process for the preparation of gabapentin (1-aminomethyl-1-cyclohexane-
acetic acid)



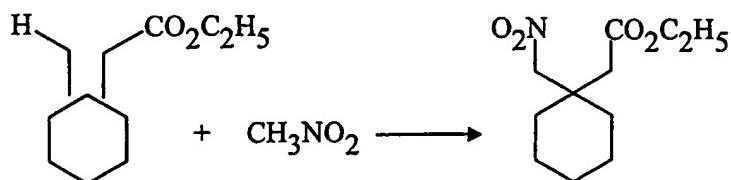
which medicament is useful, for example, in the treatment of epilepsy. The process is illustrated by the scheme:

Step (a)

10

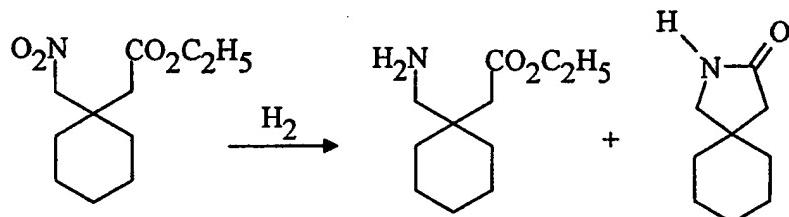


Step (b)

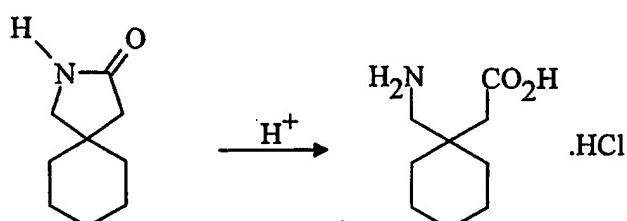


-2-

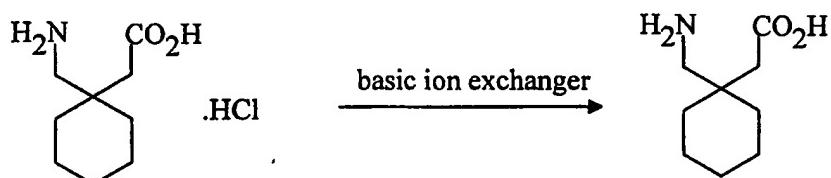
Step (c)



Step (d)



Step (e)



The instant invention provides a stereoselective synthesis for the ring-substituted analogs of gabapentin and to gabapentin itself. The advantages of the instant syntheses are: control of stereochemistry and no resolution is required at the end of the synthesis.

SUMMARY OF THE INVENTION

The invention encompasses a novel synthetic route for the preparation of substituted gabapentin analogues. The route enables the synthesis of certain single stereoisomers of individual alkylated gabapentin derivatives with a high degree of stereochemical purity.

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The invention is outlined in the general route shown below. The first step involves conversion of a substituted cyclohexanone to an α,β -unsaturated ester via use of a trialkylphosphonoacetate or an (alkoxycarbonylmethyl)triphenylphosphonium halide and a base, such as sodium hydride, potassium hydride, lithium- or sodium- or potassium-hexamethyldisilazide, butyllithium or potassium t-butoxide in a solvent such as tetrahydrofuran, dimethylformamide, diethylether, or dimethylsulfoxide at a suitable temperature in the range from -78°C to 100°C.

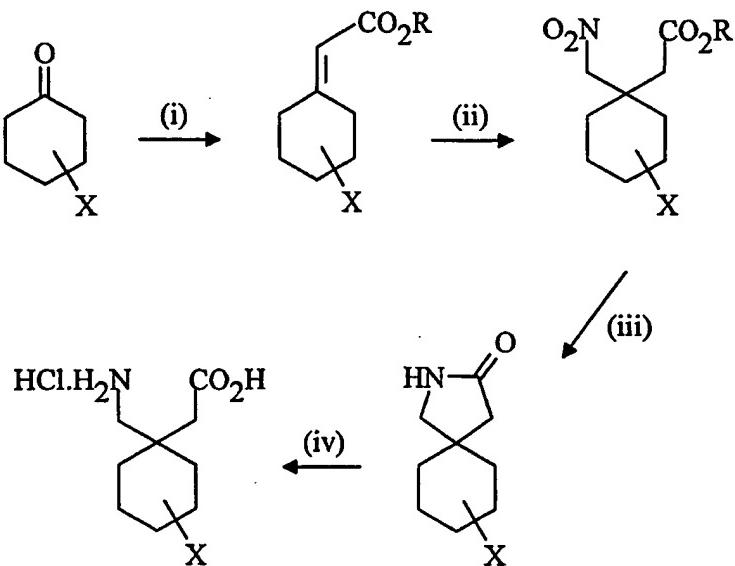
5 The second step involves reaction of the α,β -unsaturated ester with nitromethane and a suitable base such as tetrabutylammonium fluoride, tetramethylguanidine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, a sodium or potassium alkoxide, sodium hydride or potassium fluoride in a solvent such as tetrahydrofuran, diethylether, dimethylformamide, dimethylsulphoxide, benzene, toluene, dichloromethane, chloroform, or tetrachloromethane at a suitable temperature in the range from -20°C to 100°C.

10 The third step involves catalytic hydrogenation of the nitro moiety using a catalyst such as Raney nickel, palladium on charcoal or rhodium catalyst or other nickel or palladium containing catalyst in a solvent such as methanol, ethanol, isopropanol, ethyl acetate, acetic acid, 1,4-dioxane, chloroform or diethyl ether at a suitable temperature in the range from 20°C to 80°C.

15 The final step involves a hydrolysis using hydrochloric acid and may also utilize a cosolvent such tetrahydrofuran or 1,4-dioxane or other such inert water miscible solvent at a suitable temperature in the range from 20°C to reflux.

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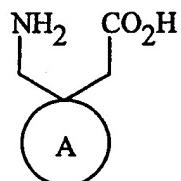
General scheme:



DETAILED DESCRIPTION OF THE INVENTION

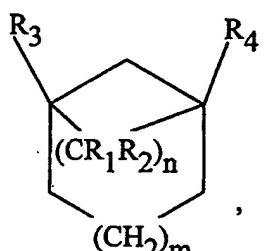
The following experimental procedures provide a novel route to be used to stereoselectively synthesize gabapentin and analogues thereof. This route provides access to pure stereoisomers.

Example 1 below shows the route used to synthesize gabapentin itself. This route is also useful in the synthesis of compounds of formula

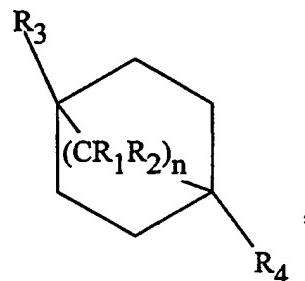


a pharmaceutically acceptable salt thereof or a prodrug thereof wherein A is a bridged ring selected from

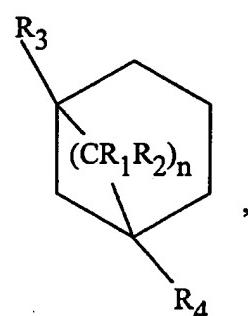
-5-



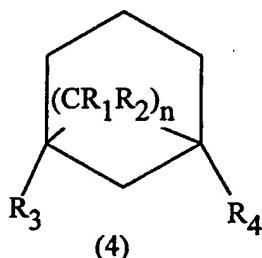
(1)



(2)

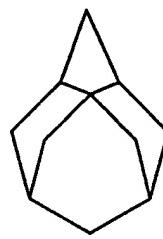


(3)



(4)

, and



(5)

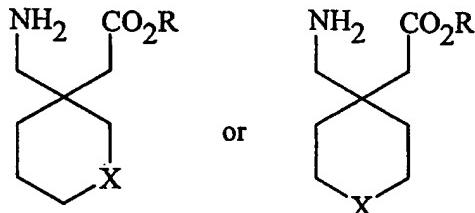
wherein

R₁ and R₂ are each independently selected from hydrogen and methyl;R₃ and R₄ are each independently selected from hydrogen or methyl;

5 n is an integer of from 1 to 4; and

m is an integer of from 0 to 2.

The route is further useful in the synthesis of compounds of formula



II

or a pharmaceutically acceptable salt thereof wherein:

10 X is O, S, S(O), S(O)₂, or NR₁ wherein R₁ is hydrogen, straight or branched alkyl of from 1 to 6 carbon atoms, benzyl, -C(O)R₂ wherein R₂ is straight or branched alkyl of from 1 to 6 carbon atoms, benzyl, or phenyl, or -CO₂R₃

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wherein R₃ is straight or branched alkyl of from 1 to 6 carbon atoms, or benzyl wherein the benzyl and the phenyl groups can be unsubstituted or substituted by from 1 to 3 substituents each independently selected from halogen, CF₃, and nitro; and

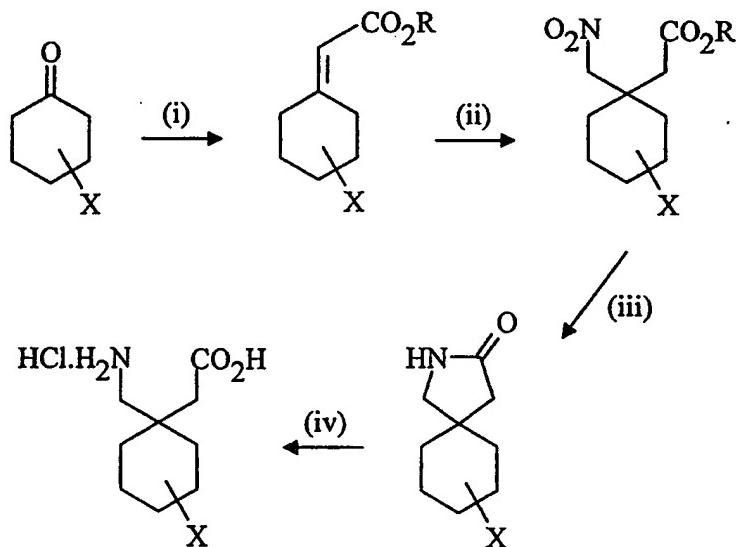
5 R is hydrogen or lower alkyl.

Example 2 below shows the use of a 4-substituted cyclohexanone to provide a pure trans gabapentin analog.

Example 3 below shows the use of a disubstituted cyclohexanone.

10 Example 4 below shows the use of a 3-substituted gabapentin analog to provide a pure cis product which is a mixture of enantiomers. The use of an enantiomerically pure 3-substituted cyclohexanone provides a pure product.

General Route

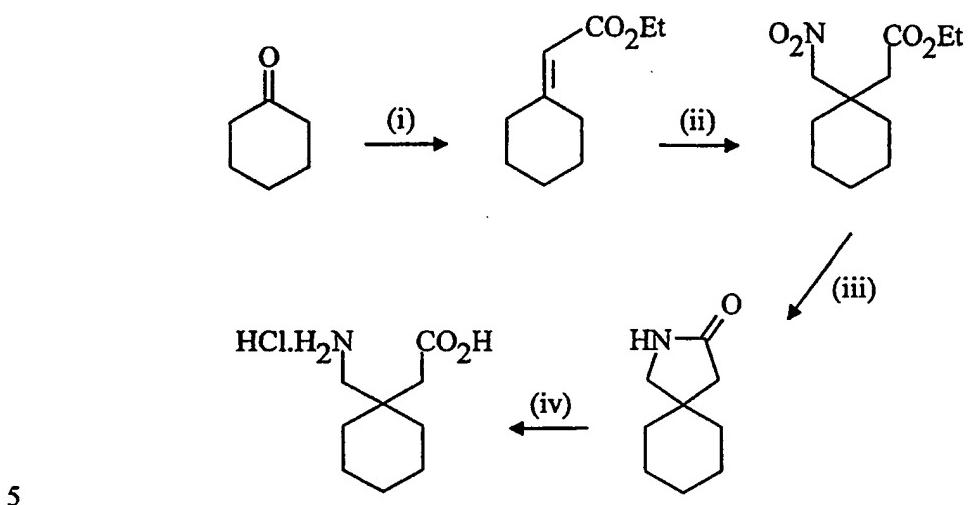


15 Reagents and conditions:

- (i) (R¹O)₂P(O)CH₂CO₂R, base (e.g., NaH, LiN(SiMe₃)₂, K₂H BuLi)
- (ii) MeNO₂, base (e.g., Bu₄N⁺F, Tetramethylguanidine, KF)
- (iii) Catalytic hydrogenation using, for example, Raney nickel or Palladium on charcoal)
- 20 (iv) Hydrolysis using HCl

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EXAMPLE 1

(i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF(ii) $MeNO_2$, $Bu_4N^+F^-$, THF, 70°C(iii) Raney Ni, H_2 , MeOH(iv) HCl/H₂O10 α,β -unsaturated ester

Sodium hydride (60% dispersion in oil, 1.16 g, 28.99 mmol) was suspended in dry tetrahydrofuran (40 mL) and cooled to 0°C. Triethyl phosphonoacetate (6.35 mL, 31.89 mmol) was added. Once the effervescence had subsided the mixture was stirred at 0°C for 15 minutes. Cyclohexanone (3 mL, 28.99 mmol) was then added and the mixture allowed to warm to room temperature. After 1 hour the mixture was partitioned between 2N HCl (50 mL) and diethyl ether (100 mL). The ether layer was collected, washed with brine, dried ($MgSO_4$), and the solvent removed in vacuo to give a clear oil which was

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purified by flash chromatography (silica, ethyl acetate:heptane 1:9) to yield 3.8 g (78%) of a colorless oil which was used without further purification.

Nitro ester

- The α,β -unsaturated ester (1.605 g, 9.55 mmol) was dissolved in tetrahydrofuran (30 mL) with nitromethane (1.03 mL, 19.1 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 14 mL, 14.0 mmol) and the resulting mixture heated to 70°C. After 18 hours the mixture was diluted with ethyl acetate (60 mL) and washed with 2N HCl (40 mL) followed by brine (40 mL). The organic phase was separated, dried ($MgSO_4$), and the solvent removed in vacuo.
- 10 The residue was purified by flash chromatography (silica, ethyl acetate:heptane, 1:9) to give 996 mg (46%) as a colorless oil.
- 1H NMR 400 MHz ($CDCl_3$) δ : 1.27 (3H, t, $J = 6Hz$), 1.38-1.62 (10H, m), 2.54 (2H, s), 4.15 (2H, q, $J = 6Hz$), 4.70 (2H, s).
- MS (ES $^+$) m/e: 230 ([MH] $^+$; 78%), 170 (100%)
- 15 IR thin film ν (cm^{-1}): 1031, 1180, 1377, 1548, 1732, 2935.
 $C_{11}H_{19}NO_4$ calculated: C, 57.63%; H, 8.35%; N, 6.11%
Found: C, 57.88%; H, 8.61%; N, 6.01%

Lactam

- The nitro ester (935 mg, 4.08 mmol) was dissolved in methanol (40 mL) and shaken over Raney nickel (catalytic) under an atmosphere of hydrogen gas (40 psi) at 35°C. After 18 hours the catalyst was removed by filtration through celite. The methanol was removed in vacuo to give 622 mg (100%) of an oil which crystallized on standing.
- 20 1H NMR 400 MHz ($CDCl_3$) δ : 1.38-1.61 (10H, m), 2.18 (2H, s), 3.14 (2H, s), 5.61 (1H, br s).
- MS (ES $^+$) m/e: 154 ([MH] $^+$; 100%)
- 25 IR thin film ν (cm^{-1}): 1252, 1451, 1695, 2925.

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C₉H₁₅NO calculated: C, 70.55%; H, 9.87%; N, 9.14%

Found: C, 70.46%; H, 9.72%; N, 8.97%

Amino Acid Hydrochloride

The lactam (608 mg, 4.0 mmol) was heated to reflux in a mixture of 6N HCl (15 mL) and 1,4-dioxan (5 mL). After 4 hours the solvent was removed in vacuo and the solid residue recrystallized from a methanol/ethyl acetate/heptane mixture to give 682 mg (71%) of a white solid.

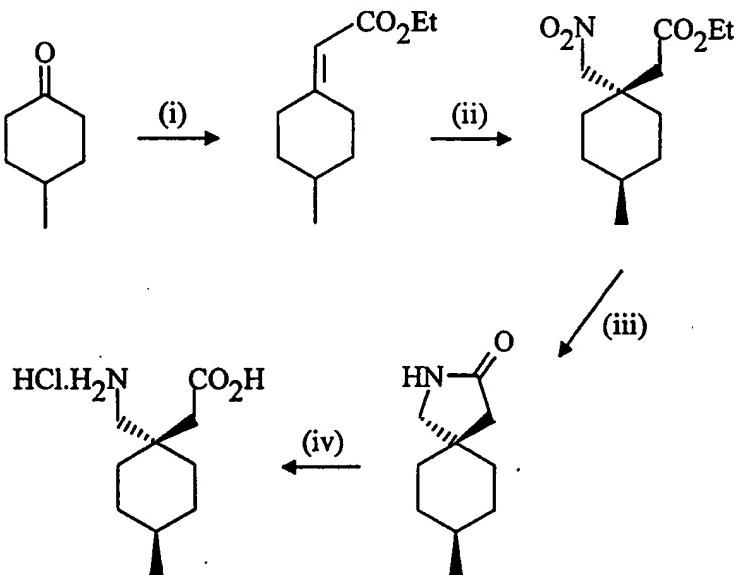
¹H NMR 400 MHz (d-6 DMSO) δ: 1.12-1.51 (10H, m), 2.41 (2H, s), 2.91 (2H, s), 8.06 (3H, br s), 12.36 (1H, br s).

MS (APCI) m/e: 172 ([MH-HCl]⁺; 100%)

C₉H₁₈NO₂Cl calculated: C, 52.05%; H, 8.74%; N, 6.74%; Cl, 17.07%

Found: C, 51.97%; H, 8.77%; N, 6.63%; Cl, 16.94%

EXAMPLE 2



- 15 (i) (EtO)₂P(O)CH₂CO₂Et, NaH, THF
(ii) MeNO₂, Bu₄N⁺F⁻, THF, 70°C

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- (iii) Raney Ni, H₂, MeOH
 (iv) HCl/H₂O

α,β -unsaturated ester

Sodium hydride (60% dispersion in oil, 0.98 g, 24.45 mmol) was suspended in dry tetrahydrofuran (50 mL) and cooled to 0°C. Triethyl phosphonoacetate (5.12 mL, 25.67 mmol) was added. Once the effervescence had subsided the mixture was stirred at 0°C for 15 minutes. 4-Methyl cyclohexanone (3 mL, 24.45 mmol) was then added and the mixture allowed to warm to room temperature. After 1.5 hours the solvent was decanted from the thick oil which had formed and the oil washed with diethyl ether (3×50 mL). The decanted solvent and the ether washings were combined and washed with 2N HCl (50 mL) followed by brine (50 mL), dried (MgSO_4), and the solvent removed in vacuo to give a clear oil which was used without purification.

Trans-Nitro ester

15 The α,β -unsaturated ester (2.94 g, 16.15 mmol) was dissolved in tetrahydrofuran (20 mL) with nitromethane (1.75 mL, 32.3 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 24 mL, 24.0 mmol) and the resulting mixture heated to 70°C. After 18 hours the mixture was diluted with ethyl acetate (60 mL) and washed with 2N HCl (40 mL) followed by brine (40 mL). The organic phase was separated, dried ($MgSO_4$), and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane, 1:9) to give 2.74 g (70%) as a colorless oil.

¹H NMR 400 MHz (CDCl_3) δ: 0.93 (3H, d, $J = 6\text{Hz}$), 1.08-1.23 (8H, m), 1.58 (2H, m), 1.73 (2H, m), 2.59 (2H, s), 4.15 (2H, q, $J = 6\text{Hz}$), 4.60 (2H, s).

25 MS (APCI) m/e: 244 ([MH]⁺; 8%), 198 (100%), 183 (68%), 168 (66%)
 IR thin film ν (cm⁻¹): 1029, 1179, 1195, 1377, 1457, 1549, 1732, 2929.
 $C_{12}H_{21}NO_4$ calculated: C, 59.24%; H, 8.70%; N, 5.76%
 Found: C, 59.00%; H, 8.73%; N, 5.70%

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Lactam

The nitro ester (2.70 g, 4.08 mmol) was dissolved in methanol (60 mL) and shaken over Raney nickel (catalytic) under an atmosphere of hydrogen gas (40 psi) at 35°C. After 18 hours the catalyst was removed by filtration through celite. The methanol was removed in vacuo and the residue purified by flash chromatography (silica, ethyl acetate/heptane 1:1) to give 721 mg (39%) of a white solid.

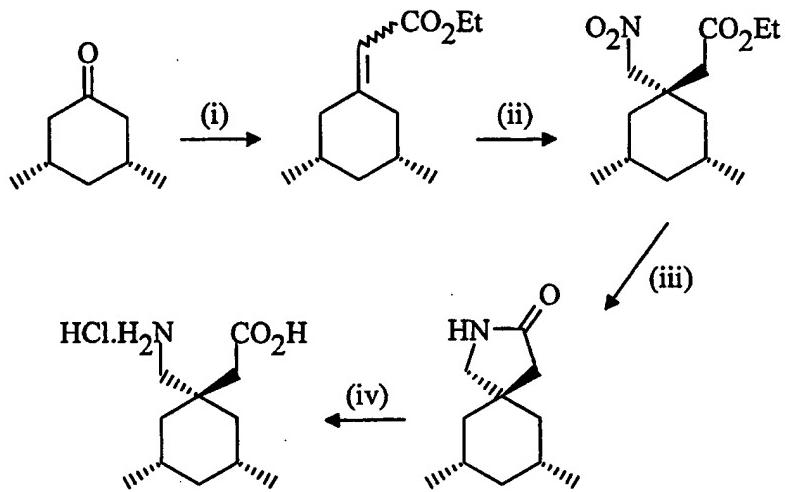
- 5 ^1H NMR 400 MHz (CDCl_3) δ : 0.91 (3H, d, $J = 6\text{Hz}$), 0.94-1.12 (2H, m), 1.25-1.43 (3H, m), 1.60 (2H, m), 1.71 (2H, br d, $J = 16\text{Hz}$), 2.21 (2H, s), 3.10 (2H, s), 5.64 (1H, br s).
- 10 MS (APCI) m/e: 168 ($[\text{MH}]^+$; 100%)
IR thin film ν (cm^{-1}): 1254, 1305, 1446, 1494, 1668, 1693, 2910, 3219.
 $\text{C}_{10}\text{H}_{17}\text{NO}$ calculated: C, 71.18%; H, 10.25%; N, 8.37%
Found: C, 71.76%; H, 10.33%; N, 8.10%

Amino Acid Hydrochloride

- 15 The lactam (715 mg, 4.0 mmol) was heated to reflux in a mixture of 6N HCl (15 mL) and 1,4-dioxan (5 mL). After 4 hours the solvent was removed in vacuo and the solid residue recrystallized from a methanol/ethyl acetate/heptane mixture to give 664 mg (70%) of a white solid.
- 20 ^1H NMR 400 MHz (d-6 DMSO) δ : 0.88 (3H, d, $J = 6\text{Hz}$), 1.10 (2H, m), 1.22 (3H, m), 1.22 (3H, m), 1.51 (2H, m), 2.43 (2H, s), 2.85 (2H, s), 7.92 (3H, br s), 12.39 (1H, br s).
MS (APCI) m/e: 186 ($[\text{MH}-\text{HCl}]^+$; 100%)
 $\text{C}_{10}\text{H}_{20}\text{NO}_2\text{Cl}$ calculated: C, 54.17%; H, 9.09%; N, 6.32%; Cl, 15.99%
Found: C, 54.33%; H, 9.38%; N, 6.32%; Cl, 15.78%

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EXAMPLE 3

(i) $(\text{EtO})_2 \text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, NaH, THF(ii) MeNO_2 , $\text{Bu}_4\text{N}^+\text{F}^-$, THF, 70°C 5 (iii) Raney Ni, H_2 , MeOH(iv) HCl/H₂O α,β -unsaturated ester

Sodium hydride (60% dispersion in oil, 1.029 g, 25.7 mmol) was suspended in dry tetrahydrofuran (50 mL) and cooled to 0°C . Triethyl phosphonoacetate (5.36 mL, 27.0 mmol) was added. Once the effervescence had subsided the mixture was stirred at 0°C for 15 minutes. Cis 3,5-dimethyl cyclohexanone (3.24 g, 25.7 mmol) was then added and the mixture allowed to warm to room temperature. After 1.5 hours the solvent was decanted from the thick oil which had formed and the oil washed with diethyl ether (3×50 mL). The 10 decanted solvent and the ether washings were combined and washed with 2N HCl (50 mL) followed by brine (50 mL), dried (MgSO_4), and the solvent removed in vacuo to give a clear oil which was used without purification.

15

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Trans-Nitro ester

- The α,β -unsaturated ester (2.08 g, 10.36 mmol) was dissolved in tetrahydrofuran (20 mL) with nitromethane (1.12 mL, 20.7 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 15.5 mL, 15.5 mmol) and the resulting mixture heated to 70°C. After 18 hours the mixture was diluted with ethyl acetate (50 mL) and washed with 2N HCl (40 mL) followed by brine (40 mL). The organic phase was separated, dried ($MgSO_4$), and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane, 1:9) to give 1.53 g (56%) as a colorless oil.
- 10 1H NMR 400 MHz ($CDCl_3$) δ : 0.80-0.98 (10H, m), 1.27 (3H, t, J = 6Hz), 1.58-1.80 (4H, m), 2.59 (2H, s), 4.15 (2H, q, J = 6Hz), 4.57 (2H, s).
MS (APCI) m/e: 258 ([MH^+]; 12%)
IR thin film v (cm^{-1}): 1028, 1182, 1377, 1461, 1549, 1732, 2954.

Lactam

- 15 The nitro ester (1.495 g, 5.8 mmol) was dissolved in methanol (60 mL) and shaken over Raney nickel (catalytic) under an atmosphere of hydrogen gas (40 psi) at 35°C. After 18 hours the catalyst was removed by filtration through celite. The methanol was removed in vacuo to give 997 mg (95%) of a white solid.
- 20 1H NMR 400 MHz ($CDCl_3$) δ : 0.52 (1H, m), 0.80-0.98 (7H, m), 1.51 (2H, m), 1.69 (4H, m), 2.20 (2H, s), 3.09 (2H, s), 6.03 (1H, br s).
MS (APCI) m/e: 182 ([MH^+]; 100%)
IR thin film v (cm^{-1}): 1258, 1278, 1324, 1373, 1432, 1456, 1679, 1693, 2908, 3208.
 $C_{11}H_{19}NO$ calculated: C, 72.88%; H, 10.56%; N, 7.73%
25 Found: C, 72.76%; H, 10.74%; N, 7.61%

Amino Acid Hydrochloride

- The lactam (981 mg, 5.4 mmol) was heated to reflux in a mixture of 6N HCl (15 mL) and 1,4-dioxan (5 mL). After 4 hours the solvent was removed

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in vacuo and the solid residue recrystallized from a methanol/ethyl acetate/heptane mixture to give 516 mg (40%) of a white solid.

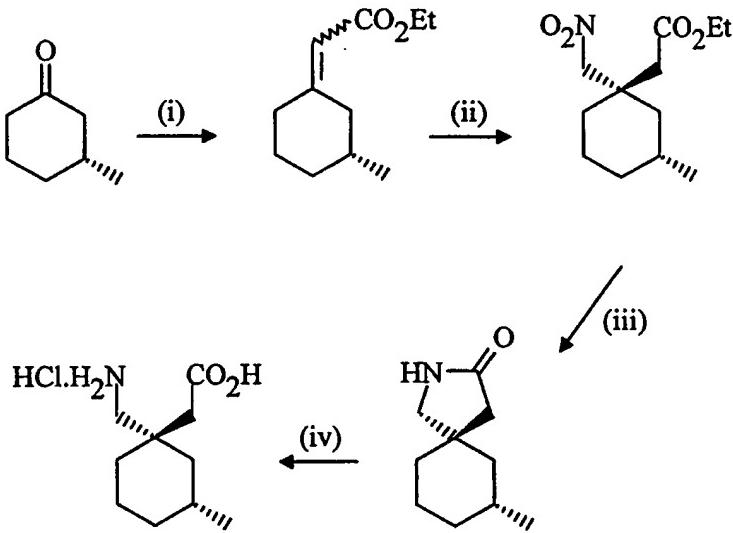
¹H NMR 400 MHz (d-6 DMSO) δ: 0.47 (1H, m), 0.77-0.91 (8H, m), 1.46-1.63 (5H, m), 2.45 (2H, s), 2.84 (2H, s), 8.00 (3H, br s), 12.37 (1H, br s).

5 MS (APCI) m/e: 200 ([MH-HCl]⁺; 100%)

C₁₁H₂₂NO₂Cl calculated: C, 56.04%; H, 9.41%; N, 5.94%; Cl, 15.04%

Found: C, 56.00%; H, 9.40%; N, 6.09%; Cl, 15.09%

EXAMPLE 4



10 (i) (EtO)₂P(O)CH₂CO₂Et, NaH, THF

(ii) MeNO₂, Bu₄N⁺F⁻, THF, 70°C

(iii) Raney Ni, H₂, MeOH

(iv) HCl/H₂O

α,β-unsaturated ester

15 Sodium hydride (60% dispersion in oil, 1.048 g, 26.2 mmol) was suspended in dry tetrahydrofuran (50 mL) and cooled to 0°C. Triethyl

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phosphonoacetate (4.76 mL, 23.9 mmol) was added. Once the effervescence had subsided the mixture was stirred at 0°C for 15 minutes. *3R* 3-methyl cyclohexanone (2.45 g, 21.8 mmol) was then added and the mixture allowed to warm to room temperature. After 1.5 hours the solvent was decanted from the
5 thick oil which had formed and diluted with diethyl ether (50 mL). The decanted solvent was washed with water (50 mL) followed by brine (50 mL), dried (MgSO_4), and the solvent removed in vacuo to give a clear oil which was used without purification.

Trans-Nitro ester

10 The α,β -unsaturated ester (2.48 g, 13.6 mmol) was dissolved in tetrahydrofuran (20 mL) with nitromethane (1.96 mL, 27.2 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 20.4 mL, 20.4 mmol) and the resulting mixture heated to 70°C. After 18 hours the mixture was diluted with ethyl acetate (50 mL) and washed with 1N HCl (2 × 25 mL) followed by brine
15 (25 mL). The organic phase was separated, dried (MgSO_4), and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, ethyl acetate:heptane, 1:10) to give 2.43 g (73%) as a colorless oil.

^1H NMR 400 MHz (CDCl_3) δ : 0.78-0.98 (4H, m), 1.27 (3H, t, $J = 6\text{Hz}$),
1.40-1.81 (8H, m), 2.61 (2H, s), 4.17 (2H, q, $J = 6\text{Hz}$), 4.58 (2H, s).

20 MS (APCI) m/e: 244 ([MH^+]; 10%)
IR thin film ν (cm^{-1}): 1027, 1097, 1155, 1190, 1378, 1457, 1549, 1732, 2929.

Lactam

The nitro ester (2.01 g, 8.28 mmol) was dissolved in methanol (30 mL) and shaken over Raney nickel (catalytic) under an atmosphere of hydrogen gas (40 psi)
25 at 35°C. After 3 hours the catalyst was removed by filtration through celite. The methanol was removed in vacuo and the residue purified by flash chromatography (silica, ethyl acetate) to give 902 mg (65%) of a white solid.

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¹H NMR 400 MHz (CDCl_3) δ : 0.77-0.96 (4H, m), 1.18-1.52 (3H, m), 1.62-1.78 (5H, m), 2.22 (2H, s), 3.08 (2H, s), 5.82 (1H, br s).

MS (APCI) m/e: 168 ($[M+H]^+$; 100%)

IR thin film v (cm⁻¹): 1252, 1455, 1698, 2920, 3220.

Amino Acid Hydrochloride

The lactam (0.858 mg, 5.1 mmol) was heated to reflux in a mixture of 6N HCl (10 mL). After 3 hours the mixture was stirred at room temperature for 18 hours. The solvent was removed in vacuo and the solid residue recrystallized from a methanol/ethyl acetate/heptane mixture to give 341 mg (30%) of a white solid.

¹H NMR 400 MHz (d-6 DMSO) δ: 0.74-0.91 (5H, m), 1.02-1.18 (1H, m), 1.38-1.65 (6H, m), 2.46 (2H, s), 2.84 (2H, s), 7.97 (3H, br s), 12.37 (1H, br s).

IR KBr disk v (cm⁻¹): 1187, 1214, 1400, 1515, 1710, 2922, 3370

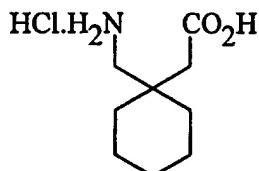
$C_{11}H_{22}NO_2Cl$ calculated: C, 54.30%; H, 9.04%; N, 6.33%; Cl, 16.06%

15 Found: C, 54.19%; H, 8.99%; N, 6.27%; Cl, 16.01%

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CLAIMS

1. A process for the preparation of a compound of formula

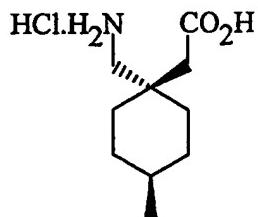


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which comprises:

- 5 a) adding cyclohexanone to a mixture of sodium hydride suspended in dry tetrahydrofuran to which triethyl phosphonoacetate was added;
- 10 b) partitioning the mixture between HCl and diethyl ether and collecting the ether layer;
- c) dissolving the product of step b) above, the α,β -unsaturated ester in THF with nitromethane and tetrabutylammonium fluoride and heating the resulting mixture to produce a nitro ester;
- d) dissolving the product of step c) above, a nitro ester in methanol and shaking over a catalyst to produce the corresponding lactam; and
- 15 e) heating the product of step d) above, a lactam, to reflux in a mixture of HCl and dioxan to produce a compound of formula I, and converting, if desired, to a pharmaceutically acceptable salt.

2. A process for the preparation of a compound of formula



II

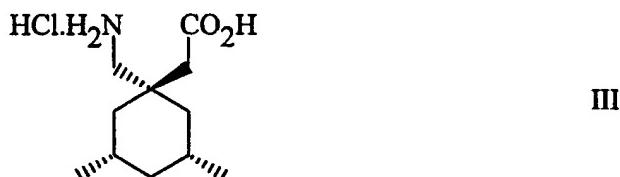
which comprises:

- 20 a) adding 4-methylcyclohexanone to a mixture of sodium hydride suspended in dry tetrahydrofuran to which triethyl phosphonoacetate was added to produce a mixture;

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- b) decanting the solvent from the mixture step a) above to produce an α,β -unsaturated ester;
- c) dissolving the ester from step b) above in nitromethane and heating the resulting mixture;
- 5 d) dissolving the nitro ester from step c) above in methanol and shaking over a catalyst to produce the corresponding lactam; and
- e) heating the product of step d) above to reflux in a mixture of HCl and dioxan to produce a compound of formula II above and converting, if desired, to a pharmaceutically acceptable salt.

10 3. A process for the preparation of a compound of formula

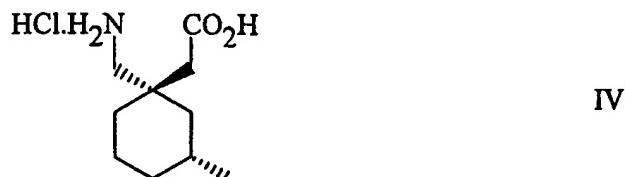


which comprises:

- a) adding cis 3, 5-dimethylcyclohexanone to a mixture of sodium hydride suspended in dry tetrahydrofuran to which triethyl phosphonoacetate was added to produce a mixture;
- 15 b) decanting the solvent from the mixture of step a) above to produce an α,β -unsaturated ester;
- c) dissolving the product of step b) above in nitromethane and heating the resulting mixture;
- d) dissolving the nitro ester from step c) above in methanol and shaking over a catalyst to produce the corresponding lactam; and
- 20 e) heating the product of step d) above, a lactam, to reflux in HCl and dioxan to produce a compound of formula III above and converting, if desired, to a pharmaceutically acceptable salt thereof.

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4. A process for the preparation of a compound of formula



which comprises:

- a) adding *3R* 3-methylcyclohexanone to a mixture of sodium hydride
5 suspended in dry tetrahydrofuran to which triethyl phosphonoacetate
was added to produce a mixture;
- b) decanting the solvent from the mixture of step a) above to produce the
corresponding α,β -unsaturated ester;
- c) dissolving the ester from step b) above in nitromethane and heating the
10 resulting mixture;
- d) dissolving the nitro ester from step c) above in methanol and shaking
over a catalyst to produce the corresponding lactam; and
- e) heating the product of step d) above to reflux in a mixture of HCl and
15 1,4-dioxane to produce a compound of formula IV above and
converting, if desired, to a pharmaceutically acceptable salt thereof.